After the table, "pH7.0" (page 30, line 10 of the provisional application) had been amended to add a space between "pH" and "7.0";
The phrase "is the mass of swollen tablet a given time...", after the "**Vt=Mt/D**" equation (page 30, line 22 of the provisional application), has been corrected to read as "is the mass of swollen tablet at a given time..." to make the phrase grammatically correct;
In the paragraph after "**Examples 3-6:**" (page 32, line 16 of the provisional application), "Formula1" has been corrected to insert a space between "Formula" and "1";
Also in the paragraph after "**Examples 3-6:**" (page 32, line 24 of the provisional application), "gent" has been corrected to read as "agent";
Between "Example 3 : **Extended Release Theophylline 80 mg**" and the table (page 32, line 30 of the provisional application), the header "**Table 2: Extended Release Theophylline**" is added for continuity in the instant application.

Besides the amendments mentioned above, the added material is identical to the provisional application. No new matter has been added. A Declaration regarding the material added by this amendment is provided herewith.

In view of the amendments and above remarks, entry of the amendments and examination of the application on the merits are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Alexander MacGreg r

Serial No.: 10/006,740

Filed: December 5, 2001

For: *HYDROSTATIC DELIVERY SYSTEM FOR CONTROLLED DELIVERY OF AGENT*

Art Unit: 3762

Examiner: Unassigned

ATTACHMENT TO THE PRELIMINARY AMENDMENT MARKED UP PARAGRAPHS AND CLAIMS (37 CFR §1.121)

IN THE SPECIFICATION:

Please amend the specification as follows:

Please amend the paragraph on page 2, lines 7-11 as follows:

Core embedding or core coated delivery systems have been disclosed, for example in U.S._3,538,214. This document describes a diffusion-controlled device in which a tablet core containing the active ingredient, is surrounded by a water insoluble coating. The insoluble film coating has been modified with modifying agents that are soluble to the external fluids in the gastrointestinal tract.

Please amend the paragraphs on page 3, line 30 through page 4, line 19 as follows:

Additionally, some active agents posses chemical properties that are comparable in ionic strengths to those of strong electrolytes and salts commonly used as osmotic adjuvants. In these instances, and due to different pH environments in the gastrointestinal tract, agents comprising significant ionic strength will manifest varying degrees of ionization that may compromise the predictable performance of the osmotic device. Osmotically active therapeutic agents with ionic strengths comparable to that of osmotic adjuvants, and that are localized within osmotically driven devices, will act as osmotic agents and

enhance the osmotic influx of water from the fluid environment. Similarly, agents having high ionic strength may also cause variations in the osmolarity of the adjacent fluid environment upon their release from the delivery device. Therefore, osmotically-driven devices comprising agents [characterised]characterized as having a high ionic strength, lack self-regulation.

A delivery system that is not readily influenced by minor changes to its physical form, intrinsic properties of an active agent (e.g. ionic strength), or variables in the environment of use (e.g. varying osmolarity of the human gastrointestinal tract and factors such as the dietary contents), can be reliably programmed to deliver the agent in a pre-determined manner with increased accuracy and precision. [therefore]Therefore, there remains within the art a need for a reliable zero-order drug delivery system, where the release of an agent is independent of its own concentration, that provides controlled drug delivery of an active agent to an environment of use and that is independent of physiological variables of the environment of use, as well as the intrinsic properties of the active agent.

Please amend the paragraph on page 13, line 27 through page 14, line 14 as follows:

Additional agents of interest include quinoline and naphthyridine carboxylic acids and related compounds, such as 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid; 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid; 5-ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-g]quinoline-7-carboxylic acid; [8-ethyl-5,8-dihydro-5-oxo-2-(1-piperazinyl)pyrido[2,3-d]pyrimidine-6-carbo xylic acid]8-ethyl-5,8-dihydro-5-oxo-2-(1-piperazinyl)pyrido[2,3-d]pyrimidine-6-carboxylic acid; [9-fluoro-6,7-dihydro-5-methyl-1-oxo-1H,5H-benzo[ij]quinoxolizine-2-carboxy lic acid]9-fluoro-6,7-dihydro-5-methyl-1-oxo-1H,5H-benzo[ij]quinoxolizine-2-carboxylic acid; 1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylic acid; 1-ethyl-1,4-dihydro-4-oxo-[1,3]dioxolo[4,5-g]cinnoline-3-carboxylic acid; 9-fluoro-3-methyl-10-(4-

methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid; 1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-1,8-naphthyr idine-3-carboxylic acid; 1-ethyl-6-fluoro-1,4-dihydro-7-(1-piperazinyl)-4-oxo-1,8-naphthyridine-3-carboxylic acid; [1-cyclopropane-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid]1-cyclopropane-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid; 1-methylamino-6-fluoro-1,4-dihydro-4-oxo-7-(4-methyl-1-ipiperazinyl)-3-qui nolinecarboxylic acid; 1-(4-fluoro-1-phenyl)-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quino linecarboxylic acid; 1-(4-fluoro-1-phenyl)-6-fluoro-1,4-dihydro-4-oxo-7-(4-methyl-1-piperazinyl)-3-quinolinecarboxylic acid; [1-(4-fluoro-1-phenyl)-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-nap hthyridine-3-carboxylic acid]1-(4-fluoro-1-phenyl)-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid; and 1-ethyl-6-fluoro-1,4-Dihydro-4-oxo-7-(3-ethylaminomethyl-1-pyrrolidinyl)-8-fluoro-3-quinolinecarboxylic acid.

Please amend the paragraph on page 17, lines 7-16 as follows:

- acrylic-acid polymers with cross-linking derived from allylsucrose or allylpentaerithritol, including water-insoluble acrylic polymer resins. Single compounds or a blend of compounds from this group of polymers include for example, but not limited to Carbopol.RTM.971-P, Carbopol.RTM.934-P, Carbopol.RTM.974P and Carbopol.RTM.EX-507 (GF Goodrich, or any other commercially available brand with similar properties, may be used). [Prefereably]Preferably, the acrylic-acid polymers have a viscosity from about 3,000 centipoise to about 45,000 centipoise at 0.5% w/w concentration in water at 25°C, and a primary particle size range from about 3.00 to about 10.00 microns in diameter, as determined by Coulter Counter;

Please amend the paragraph on page 17, line 31 through page 18, line 9 as follows:

Examples of methods of preparation, for example of Carbopol.RTM.934-P, - a polymer of acrylic acid lightly cross-linked with polyallyl ether of sucrose having an average of 5.8 allyl groups per each sucrose molecule, has been disclosed in U.S. 2,909,462; 3,033,754; 3,330,729; 3,458,622; 3,459,850; and 4,248,857 (which are incorporated herein by reference). When Carbopol.RTM.971-P is used, the preferred viscosity of a 0.5% w/w aqueous solution is 2,000 centipoise to 10,000 centipoise. More preferably, the viscosity of a 0.5% w/w aqueous solution is 3,000 centipoise to 8,000 centipoise. When Carbopol.RTM.934-P is used, the preferred viscosity of a 0.5% w/w aqueous solution is 20,000 centipoise to 60,000 centipoise, more preferably, the viscosity of a 0.5% w/w aqueous solution is 30,000 centipoise to 45,000 centipoise.

Please amend the paragraph on page 19, lines 15-20 as follows:

- single compounds or combinations derived from cross-linked N-vinyl-2-pyrollidone (PVP) selected from a group of chemically identical polyvinylpolypyrrolidone such as Polyplasdone.RTM.XL, Polyplasdone.RTM.XL-10, Polyplasdone.RTM.INF-10 (International Specialty Products). [Prefreably]Preferably, the cross-linked N-vinyl-2-pyrollidone has a particle size from about 9 microns to about 150 microns; and

Please amend the paragraph on page 24, lines 13-22 as follows:

Without wishing to be bound by theory, at a given point of net imbibed water, there is a given ratio of the number of hydrated group-A particles and expanded particles or molecules of the rapid expansion-group-B particles, that creates a positive differential [pressure .]pressure. This hydrostatic pressure acts against the influx of water and at some point the inflow of water will equal the outflow of water. The resultant hydrostatic volume efflux overwhelms the passive diffusive volume efflux within the delivery system. When the inflow and outflow of water become equal, the system manifests a dynamic constant

volume and surface area. This results in a steady state release of solved or partially solved particles of the agent of interest along with any other adjuvant.

Please amend the paragraph on page 25, lines 11-31 as follows:

In the hydrostatic delivery system of this invention, the presence of a hydrostatic couple creates a positive hydrostatic pressure within the delivery system as a result of the differential rates of volume expansion between the group-A and group-B components. This differential pressure opposes the volume influx of the imbibed fluid and reduces the volume gain of delivery system. The volume efflux due the hydrostatic pressure $(dV/dt)_h$, is substantially greater than the contribution to volume efflux as a result of passive diffusive flux. At an optimal level, which may be determined by a mathematically predictable ratio of the components of the hydrostatic couple, the rate of volume efflux approaches and eventually equals the rate of volume influx. This represents a dynamic steady state with a zero net increase in volume and a constant surface area of the delivery system (see Figure2). The one or more agents of interest that are dissolved or partially solved within the delivery system, are thus released at a rate determined by the total (net) efflux controlled and determined by hydrostatic pressure within the delivery system. The insignificance of the passive diffusive contribution to the net volume efflux proffers a delivery system whose performance is independent of the chemical concentration gradient of the agent of [intrest]interest. If the volume within the delivery system is such that the total concentration of the agent of [interst]interest is above its saturation concentration, the resultant release of the agent of interest will exhibit a zero or near zero order kinetics. The net volume flux in the hydrostatic delivery system is represented by the following equation (equation 2):

IN THE ABSTRACT:

Please amend the abstract on page 40, lines 6-9 as follows:

The present invention provides a hydrostatic delivery system comprising a hydrostatic couple and an agent of interest. The hydrostatic couple comprises,

at least one hydrodynamic fluid-imbibing polymer, and at least one hydrostatic pressure modulating agent. This delivery system has the ability to control the release of one or more agents of interest within a fluid environment following zero-order kinetics.

IN THE CLAIMS:

Please amend claim 11 as follows:

11. The hydrostatic delivery system according to claim_1 wherein the agent of interest comprises a plurality of discrete active particulates.